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Role of Adipoq Rs 266729 Gene Polymorphism with Risk of Type 2 Diabetes Mellıtus: Case Control Study

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Abstract
Objectıve: The aim of the study is to reveal the relationship between adiponection gene variants type 2 diabetes, in diabetes, which has become a majör problem in the twenty-first century. **Materıals and Methods:** This case-control study included 100 patients (60 men and 40 women) with type 2 diabetes treated at Musayyib Hospital and 100 healthy volunteers of the same age and gender to serve as a control group for the study. In the study, DNA was extracted from blood and genotyped by PCR-RFLP and also clinical features of diabetes (Fasting glucose, HbA1c and Lipid profile) were investigated. **Results:** Compared to patients without diabetes, the frequency of the G allele of the rs266729 polymorphism was found to be significantly higher in diabetic participants. In addition, the homozygous GG genotype greatly increased the risk of Type II diabetes. **Conclusıon:** The heterozygous genotype (GC\CG) was associated with a twofold increased risk of type II diabetes compared to the wild type (CC), and although there was no significant difference in the clinical features of diabetes according to adiponectin genotypes, there was a significant difference in fasting glucose, HbA1c and lipid profile between patients and controls. In the Iraqi population, the adiponectin gene polymorphism rs266729 has been linked to Type II diabetes, with people with the heterozygous genotype (GC\CG) being significantly more likely to develop Type II diabetes.
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1. Introduction

Diabetes mellitus (DM) is a metabolic condition that progresses in the body as a consequence of a reduction in insulin action or insulin production. Inevitably, as the condition progresses, pathological modifications, including such as nephropathy, retinopathy, in addition cardiovascular complications, arise in the body. Type I DM plus type II DM are two greatest common subtypes of the diabetes (Padhi *et al.* 2020). Diabetes is one of the most difficult health concerns facing society in the twenty-first century. It is estimated that Type II diabetes mellitus (T2DM) presentation for ninety–ninety-five percent of entirely diabetic cases. It manifests itself in a variety of ways, tend to range from primarily resistance to insulin combined with insulin deficiency to mainly an insulin secretory imperfection joints with resistance to insülin (Cho *et al.* 2018).

In most parts of the world, diabetes is becoming more common. It has been predicted that five hundred and fifty-two million persons would develop diabetes disease through 2030, according to the World Health Organization (WHO) (Meshkani and Adeli 2009). Several studies have proven that type 2 diabetes is caused by the interplay of several risk factors of the genetic as well as environmental, for example age, sex, ethnicity, way of life, as well as obesity, among other things (Murea *et al.* 2012). Globe, it presently affects approximately 317 million of people, but its occurrence in many countries, including Iraq, is expanding quickly due to population growth as well as a rise in obesity rates (Shaw *et al.* 2010). Adipokines, which are bioactive chemicals secreted by adipose tissue and include adiponectin, are among the compounds produced (Haghighatdoost *et al.* 2020).

This protein, according to its biological activities, which include insulin sensitization, anti-inflammatory, and antioxidant capabilities, may be involved in the development of type 2 diabetes with insulin resistance (T2DM and insulin resistance) (Lim *et al.* 2014). Adiponectin is a protein containing twenty hundred and twenty-four amino acids that is generated by cells of the white adipose (fatty tissue) (Dietert and Dietert 2010). The adiponectin construction is composed of the single-chain trimers, which are comprised of a changeable N-terminal domain, collagen domain as well as globular domain at C-terminus. Pro104-Tyr109 is a hinge protein that connects two monomers that are adjacent to each other, forming three spherical domains that are located through the End-N besides C ends (2 monomers that are near to the one another). The hinge of Pro104-Tyr109 acts like a connection among the both monomers. Approximately ten twisted threads are contained within each spherical component of single-chain trimmer, which is protected via a bell-shaped framework. It can be found in the form of a trimer, hexamer, or multimer structure. In addition, it has been referring to that the longitudinal form is unusual observed in normal circumstances due to great instability of thermodynamic, nevertheless that disintegration products of

protein (which comprise the globular endspin domain) is discovered inside human body (De Luis *et al.* 2020). An adiponectin molecule has three distinct molecular weights and can be detected in three main configurations: a low, moderate and high- molecular weight (Hara *et al.* 2006). ADIPOQ is the gene that encodes for adiponectin, which is found on the chromosome- 3q27 and distances a total of sixteen kb of the sequence of genomic. Adiponectin is a hormone that regulates fat metabolism. Recently, certain human investigations have indicated that this chromosome region is susceptibility locus intended for type 2 diabetes as well as coronary heart disease (CHD) (Mohammadzadeh and Zarghami 2009).

One polymorphism, rs266729, which is a silent C to G substitution located in the proximal promoter, has been extensively explored by epidemiological research. A prior research reveals thirteen SNPs through testing mutation in gene of the adiponectin in both French as well as Japanese communities (Li *et al.* 2013). Several research has found that the variant alleles located at the rs266729 as well as rs150129 polymorphisms are often related with type II diabetes, resistance to insulin in addition other metabolic disorders (Hsiao and Lin 2016).

The purpose of this study was to evaluate the link between adiponectin gene polymorphisms (rs266729) and patients suffering from type II diabetes mellitus in Iraq.

2. Materıals and Methods

This case-control research was conducted concurrently across the time span of September 2022 until March 2022, will include on hundred patients (sixty males and fourty females) suffer from type 2 diabetes mellitus who are undergoing medical follow-up at Musayyib General Hospital, and 100 sex-age matched volunteers are healthy individuals as a standard group for study. In order to participate in the research, participants gave their verbal permission. The information was gathered by conducting direct interviews with each participant. This study is a master's thesis. Permission has been obtained by Iraq the General Secretariat of the Hol Hussein Shrine Health and Medical Education Authority in accordance with the Ethics guidelines (20.03.2022) for biomedical and health research on human participants.

Collection of blood specimens: 0,5 mL of bloodstream were collected from each participant and then split evenly between two test tubes. The initial 3 mL was poured into the gel tube comprising clot activator and allowed to coagulate for about 10 minutes at RT previously centrifugation (ten min at four-thousand rpm). The serum was also divided into Eppendorf tubes as well as stored at minus 20°C even total cholesterol, then triglycerides, blood glucose, and the low, high and very low-density lipoprotein concentrations were identification. The another two mL was diffused to the EDTA tube to measurement of HbA1c and DNA extraction to identify adiponectin polymorphisms (rs 266729) by (PCR-RFLP).

2.1. Statistical Analysis

Microsoft Excel 2013 and the statistical package for social sciences (SPSS) 21,0 were used to conduct the statistical analysis for this prospective research. The mean and standard deviation were used to describe numerical data. The t-test on an independent sample is used to compare the two groups. ANOVA is a statistical method used to compare three groups against one another. The Chi-square test was performed to characterize the connection between the variables, and the categorical data were reported as counts and percentages. The odds ratio as well as the confidence interval for it at 95 percent were used to evaluate the possible risk of mutation associated with the research group. A statistically significant difference is considered to exist if it is either equal to or lower than the 0.05 threshold.

3. Results

In this particular research, there were a total of 100 participants, each of whom had diabetes, as well as 100 controls who seemed to be in good condition. When comparing the two groups in terms of their average ages, there was no discernible difference among them (56.99±8.60 years for patients and 58.28±8.54 years for controls). In addition, a p-value analysis revealed no statistically significant differences among groups (0.291).

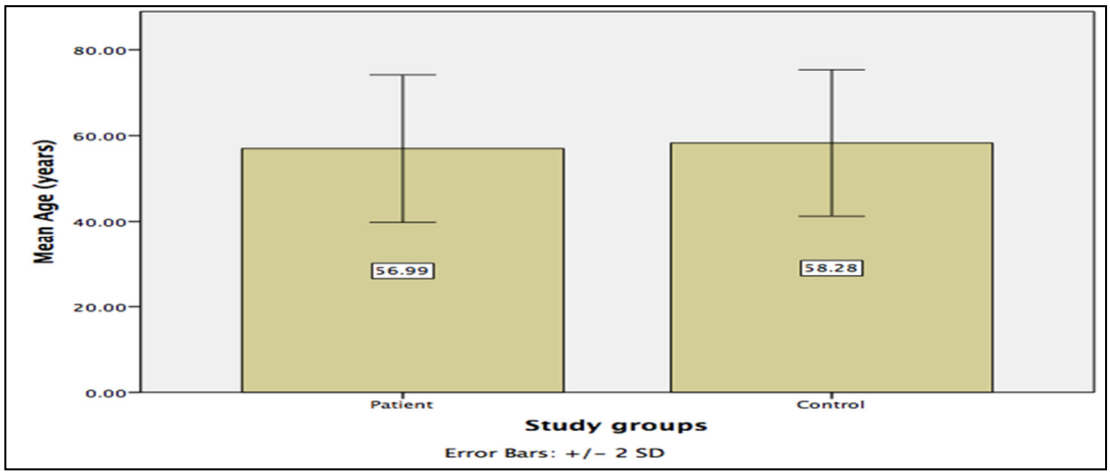

Figure 1 Displays the average ages of both groups

Table 1. Emerges the sex distribution of both the patients and the controls

		Study groups		P-value
		Patient	Control	
Sex	Male	54	59	0.182^{NS}
		54.0%	59.0%	
	Female	46	41	
		46.0%	41.0%	
	Total	100	100	

Patients with diabetes had significantly higher mean fasting blood sugar levels compared to healthy persons (159,13±5.67 vs 87.08±5.83 mg/dL), and the p-value for this comparison was significantly lower than (<0.001**), indicating a significant difference among the study two groups. This demonstrated that there was a substantial difference among the study two groups with regard to the concentration of glucose in the serum obtained from fasting blood over the course of this particular investigation. As may be seen in the following illustrations.

Table 2. Comparative fasting blood sugar levels among the groups

	Study groups	Mean	Std. Deviation	P value
Fasting blood sugar (mg/dL)	Patient	159.13	5.67	<0.001**
	Control	87.08	5.83	

Table 3. HbA1c levels across all of the study groups

	Study groups	Mean	Std. Deviation	P value
HbA1C (%)	Patient	7.86	0.39	<0.001**
	Control	5.03	0.29	

Table 4. Concentrations of cholesterol in the blood of patients compared to those of controls

	Study groups	Mean	Std. Deviation	P value
Cholesterol (mg/dL)	Patient	293.12	19.51	<0.001**
	Control	174.32	15.97	

Table 5. The quantity of triglycerides in the serum across the study participants

	Study groups	Mean	Std. Deviation	P value
Triglyceride (mg/dL)	Patient	221.36	11.87	<0.001**
	Control	93.12	15.25	

Table 6. Low lipoprotein serum concentration among groups

	Study groups	Mean	Std. Deviation	P value
Low Density Lipoprotein (mg/dL)	Patient	224.57	18.91	<0.001**
	Control	116.63	15.62	

Table 7. High density lipoprotein levels among groups

	Study groups	Mean	Std. Deviation	P value
High Density Lipoprotein (mg/dL)	Patient	24.27	4.26	<0.001**
	Control	39.06	6.14	

Table 8. Very density lipoprotein serum concentration among both groups

	Study groups	Mean	Std. Deviation	P value
Low Density Lipoprotein (mg/dL)	Patient	224.57	18.91	<0.001**
	Control	116.63	15.62	

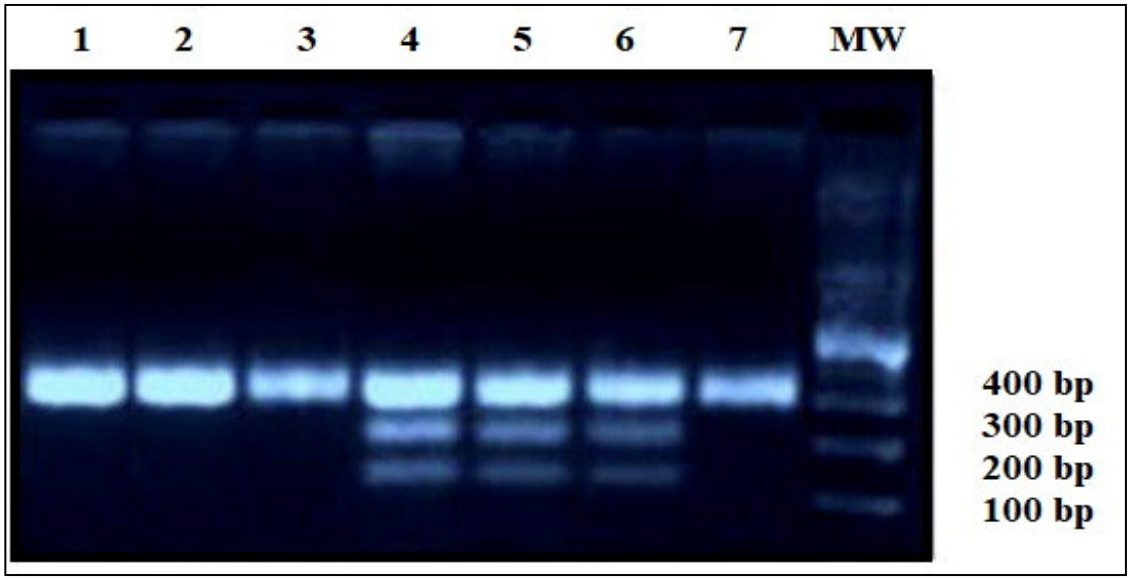

Figure 2.Gel electrophoresis for Adiponectin SNP (rs266729) PCR products, CC genotype lane 1, 2, 3 size of product is 334 bp, genotype GG and GC line 4, 5, 6, 7 size of product is 334/212/122 bp

3.1. Association of (rs266729) of Adiponectin with Study Groups

The G>C allele was present in the adiponectin single nucleotide polymorphism rs266729, which has three genotypes: homozygous genotype (GG), wild genotype (CC), as well as heterozygous genotype (GC\CG). Table 4.10 demonstrated that the heterozygous genotype frequency (GC\CG) had the highest frequency in 42 (42%) diabetic patients compared to a lower frequency in the control group 24 (24%), whereas wild genotype (CC) had the lowest frequency (47%) in 47 patients with diabetes compared to the highest frequency in 68 (68%) among the healthy control group, in addition, the Homozygous genotype frequency (GG) was present in 11 (11%) of diabetic patients in comparison to 8 (8%) of the healthy control group. The findings demonstrated a statistically significant disparity for genotype (GC\CG) among diabetic incomparaple with control groups (P-value=0.002), and an additional statistically significant difference for allele frequencies between diabetic patients and control healthy groups (P-value=0.004) as shown in Table 8.

Table 9. A prevalence of the adiponectin gene's (rs266729) genotypes and allelic variants throughout the research groups

		Study groups		P value	Odds ratio (95% CI)
		Patient	Control		
rs266729 Genotype	GG	11	8	0.214	-
		11.0%	8.0%		
	GC/CG	42	24	0.002	
		42.0%	24.0%		
	CC	47	68	-	
		47.0%	68.0%		
rs266729 Allele	G allele	64	40	0.004	1.88 (1,1-2.9)
		32.0%	20.0%		
	C allele	136	160		
		68.0%	80.0%		

The Odds ratio was calculated keeping CC (wild type) as a baseline. The significance odds ratio for GC\CG (heterozygous genotype) was 2.53 and GG (homozygous) was 1.99, whereas the odds ratio for (G) allele frequency was 1.88 as shown in Table 9 Gel electrophoresis of PCR product for Adiponectin genes are shown in Figure 9.

3.2. Association Between Diagnostic Parameters of T2DM and Genotypes of the Adiponectin Gene (rs266729)

The clinical features of the research individuals are broken down in respec to the genotypes of the rs266729 variant of adiponectin gene. It showed that there were no differences in means, and there were also no significant variances in any of the parameters with regard to the adiponectin genotypes.

Table 10. Clinical features of individuals with type 2 diabetes based on rs266729 genotype of adiponectin gene

		Patient		
		rs266729 Genotype		
		GG	GC/CG	CC
Fasting blood sugar (mg/dL)	Mean	160.18	159.52	158.53
	SD	5.56	6.17	5.27
P value		0.581^{NS}		
HbA1C (%)	Mean	7.74	7.87	7.89
	SD	.48	.39	.39
P value		0.537^{NS}		
Cholesterol (mg/dL)	Mean	291.09	292.93	293.77
	SD	17.78	21.67	18.19
P value		0.918		
Triglyceride (mg/dL)	Mean	221.00	221.43	221.38
	SD	9.36	13.75	10.75
P value		0.994		
High Density Lipoprotein (mg/dL)	Mean	22.00	24.69	24.43
	SD	5.08	4.02	4.21
P value		0.167		
Low Density Lipoprotein (mg/dL)	Mean	224.89	223.95	225.06
	SD	17.28	21.68	16.89
P value		0.962		
Very Low Density Lipoprotein (mg/dL)	Mean	44.20	44.29	44.28
	SD	1.87	2.75	2.15
P value		0.994		

4. Discussion

Throughout our study patients with diabetes had significantly higher mean fasting blood sugar levels compared to healthy persons (159.13±5.67 vs 87.08±5.83 mg/dL), and the p-value for this comparison was significantly lower than (<0.001**), indicating a significant difference between both groups. This demonstrated that there was a substantial disparity between study groups with regard to the concentration of glucose in the serum obtained from

fasting blood over the course of this particular investigation. The results of this study, which were based on fasting glucose serum concentration, were in agreement with our study's findings, which showed that patients with diabetes had a significantly higher mean of th blood glucose level than control group(El-Shal *et al.* 2014; Ali *et al.* 2016).

The much lower p-value for this comparison (0.001**) indicates that there was a significant troupes between study groups, with diabetes patients having mean HbA1c values that were significantly higher than those of healthy people (7.86±0.39 vs. 5.03±0.29 percent). This demonstrated that there was a significant variation in the concentration of HbA1c among both groups during the course of the investigation. Another Iraqi study that agrees with our findings is the one that included three studied groups: the first group consisted of twenty healthy control subjects, then second group contained of type 2 diabetic patients with controlled lipidemia, and the third group consisted of type 2 diabetic patients who had dyslipidemia. The glycated hemoglobin (HbA1c) reported a marked increase in both diabetic groups when compared to the healthy group (Mahmmod and Hussein 2017). Baghdad city was the location of an additional research that was done in Iraq and came to the same conclusion: the glycated hemoglobin HbA1c concentration was substantially higher in diabetics than in the apparently healthy group (Mohammed *et al.* 2021).

Diabetes mellitus raises one's likelihood of developing atherosclerotic vascular disease. People who have additional recognized risk factors, like dyslipidemia, elevated blood pressure, smoking, or obesity, are at a greater risk than those who do not have any of these things (Ahmed *et al.* 2008). Patients who have type 2 diabetes have a drastically increased opportunity of developing accelerated cerebral and peripheral vascular disease, as well as a two- to four fold growing risk of developing cardiovascular disease (CVD). In point of fact, between 75 and 80 percent of diabetic adults die away as a result of either one of these illnesses or a combination of these disorders (Nakhjavani *et al.* 2006). HDL was higher in control than patient groups, and the p-value for this comparison was significantly lower than (0.001**), which suggests that there was a significant dissimilarity between the groups. Patients who had diabetes had significantly higher mean lipid profile levels (cholesterol, triglycerides, LDL, and VLDL-cholesterol) compared to healthy people. During the course of this investigation, the findings demonstrated that there was a substantial gap between the two groups in terms of the concentration of lipid profiles that were found in the blood. This was shown by the fact that the results of this demonstrated this disparity. In yet another case-control research conducted in Iraq, fifty people with type II diabetes were compared to fifty healthy persons for the purpose of determining the blood levels of lipid profile. According to the findings of this study, the concentrations of triglycerides, total cholesterol, low-density and very low-density lipoprotein cholesterol, as well as the LDL /HDL- Cholesterol ratio all showed significant increases (p 0.01), whereas the levels of serum HDL-cholesterol showed significant decreases (p 0.01) among the participant groups (Al-Fartosy *et al.* 2017). An additional study carried out in Erbil, Iraq, agrees with the consequnces of this study, which demonstrated that the median serum levels of total cholesterol, triglycerides, and LDL-cholesterol in patients with uncontrolled diabetes were considerably higher than those of patients with stable diabetes (Ismail 2014).

The findings of a previous study that was performed on a total of one hundred and twenty clinically identificated T2DM participants categorized into sixty obese T2DM and sixty non-obese T2DM males) as well as sixty apparently healthy males serving as the control also coordinated with the findings of our study, which showed that there were significant variation in lipid profile in between obese T2DM, the non-obese T2DM, as well as the control groups (Al-Tuâ and Obed 2018). These findings may be elucidated by the actuality that people with type 2 diabetes have a greater occurence of the lipid profile abnormalities, which lead to greater rates of coronary artery disease in such individuals.

4.1. Distribution of (rs266729) of Adiponectin Among Study Groups

Numerous studies have shown that type 2 diabetes is the consequence of the interact among certain genetic risk factors plus environmental risk variables, including age, gender, race, life choices, as well as obesity (Murea *et al.* 2012). This current study demonstrated that the heterozygous genotype frequency (GC\CG) had the highest frequency in 42 (42%) diabetic patients compared to a lower frequency in the control group 24 (24%), whereas wild genotype (CC) had the lowest frequency (47%) in 47 patients with diabetes compared to the highest frequency in 68 (68%) among the healthy control group, in addition, the homozygous genotype frequency (GG) was present in 11 (11%) of diabetic patients in comparison to 8 (8%) of the healthy control group. The findings demonstreated a statistically important difference for genotype (GC\CG) among diabetic and control groups (P-value=0.002), and an additional statistically significant difference for allele frequencies among diabetic patients in contrast control healthy groups (P-value=0.004). The Odds ratio was calculated keeping CC (wild type) as a baseline. The significance odds ratio for GC \ CG (heterozygous genotype) was 2.53 and GG (homozygous) was 1.99, whereas the odds ratio for (G) allele frequency was 1.88. Another previous Iraqi study also investigated the linked between adiponectin (rs266729) gene polymorphism and type two diabetes mellitus. After taking into account factors such as age, gender, and body mass index, the results of the study revealed that individuals with the homozygous genotype (GG) had a three times increased risk of acquiring type 2 diabetes when compared with those with the

wild type (CC). Additionally, the risk in heterozygous (CG) genotype carriers was two folds higher than (Kaftan and Hussain 2015). The conclusions presented here are in line with the findings obtained from two other Arab groups, namely Jordanians as well as Tunisians (Alkhateeb *et al.* 2013, Mtiraoui *et al.* 2012). A further research from the past looked at the number of alleles and the distribution of genotypes in the rs266729 polymorphism in people with type 2 diabetes and control persons. In patients with type 2 diabetes, the prevalence of the (GG and GC+ CG) genotype as well as G allele vs. C allele) was much greater than in healthy participants, as shown by the findings of the research (Alimi *et al.* 2021). In order to understand how the rs266729 variant of the adiponectin gene contributes to the development of type 2 diabetes, one must concentrate on the molecular pathways. One research found that Sp1 was connected with the adiponectin gene promoter, and that over-expression of Sp1 increased the activity of gene promoters (Berg *et al.* 2002). In a separate piece of research, it was discovered that the minor allele G of rs266729 changes the DNA sequence of the SP1 binding site of the transcriptional elements. This leads to a decrease in the amount of transcriptional activity produced by the adiponectin gene promoter. Therefore, when the expression of the adiponectin gene is adversely regulated, fewer plasma levels of adiponectin are produced, which in turn elevated the risk of type 2 diabetes and obesity (Suriyaprom *et al.*2014). These data provided strong evidence that the rs266729 polymorphism in the adiponectin gene had an impact in the development of type 2 diabetes in Iraqi individuals. This effort may improve the strategies for the prevention, diagnosis, as well as the therapies of diabetic patients throughout Iraq since the recognition of genetic variants that attempt to impact type 2 diabetes is a major area of investigation that aims to comprehend the mechanisms that underlie the pathophysiological aspects of this illness as well as the possible implications.

4.2. Clinical Features of T2DM Patients Based on Genotypes of the Adiponectin Gene (rs266729)

The clinical features of the research individuals are broken down according to the genotypes of the rs266729 variant of the adiponectin gene, it showed that there were no differences in means, and there were also no significant variances in any of the parameters with regard to the adiponectin genotypes throughout this current study. A prior research that was carried out in Iraq analyzed the connection of clinical features of study participants in respect to the adiponectin gene rs266729 genotypes. The findings of this study indicated that this polymorphism has a substantial influence on HDL levels. Despite the fact that there was no discernible difference between these genotypes and another marker (Kaftan and Hussain 2015). A second investigation was conducted in which the same biochemical marker was analyzed in connection to adiponectin polymorphism. This study came to the conclusion that there was no link between the rs266729 polymorphism and either the pre-treatment or post-treatment biochemical measures (De Luis *et al.* 2018).

5. Conclusion

A functional structure made up of holons is called holarchy. The holons, in coordination with the local environment, function as autonomous wholes in supra-ordination to their parts, while as dependent parts in subordination to their higher level controllers. When setting up the WOZIP, holonic attributes such as autonomy and cooperation must have been integrated into its relevant components. The computational scheme for WOZIP is novel as it makes use of several manufacturing parameters: utilisation, disturbance, and idleness. These variables were at first separately forecasted by means of exponential smoothing, and then conjointly formulated with two constant parameters, namely the number of machines and their maximum utilisation. As validated through mock-up data analysis, the practicability of WOZIP is encouraging and promising.

Suggested future works include developing a software package to facilitate the WOZIP data input and conversion processes, exploring the use of WOZIP in the other forms of labour-intensive manufacturing (e.g. flow-line production and work-cell assembly), and attaching a costing framework to determine the specific cost of each resource or to help minimise the aggregate cost of production.

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